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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 09/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,664	SHEN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-25 are pending.

Applicants' amendment filed July 24, 2006 is acknowledged. Applicants' response has been fully considered. Claims 1, 2, 10, 17, 21, 23 and 25 have been amended. Claims 19 and 20 are non-elected invention and withdrawn from consideration. Therefore, claims 1-18 and 21-25 are examined.

Withdrawn Informalities

2. The previous objection to specification, regarding the sequences and Figs 2 and 3, is withdrawn in view of applicants' amendment to the specification, and applicant's response at page 12 in the amendment filed July 24, 2006.

Withdrawn Claim Objection

3. The previous objection to claims 1, 2, 10, 17, 21, 23 and 24, regarding the "SEQ ID NO:", is withdrawn in view of applicants' amendment to the specification, and applicant's response at page 12 in the amendment filed July 24, 2006.

Withdrawn Claim Rejections -35 USC § 112

4. The previous rejection of claims 1-9, 17, 18 and 21-25 under 35 U.S.C. 112, second paragraph is withdrawn in view of applicants' response at page 20 in the amendment filed July 24, 2006.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method of modifying a biological molecule as a substrate by formation of C-O bond, or a method of producing a specific macrotetralide (compounds **1-5**, Fig. 11) using a specific acyl-CoA such as 6-CoA or 8-CoA as a substrate, comprising contacting the substrate with a polypeptide selected from the group consisting of: the polypeptide of SEQ ID NO:3 or 5, and a polypeptide encoded by the nucleotide sequence of SEQ ID NO:1, 2 or 4, does not reasonably provide enablement for a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide consisting of an amino acid sequence set forth in SEQ ID NO:3 or 5 (reads as a polypeptide containing the full length or a fragment of SEQ ID NO:3 or 5; the amino acid sequence set forth in SEQ ID NO:3 or 5 refers to the full length of SEQ ID NO:3 or 5); a polypeptide encoded by a nucleic acid consisting of a nucleotide sequence set forth in SEQ ID NO:1, 2 or 4 (reads as a polypeptide encoded by the full length or a fragment of SEQ ID NO:1, 2 or 4); and a polypeptide encoded by a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation (reads the peptide may have the activity of C-O formation), wherein the macrotetralide is not identified, and the function and sequence of the fragment are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-18 and 21-25 are directed to a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological

molecule (a substrate) with a polypeptide selected from the group consisting of: a polypeptide consisting of an amino acid sequence set forth in SEQ ID NO:3 or 5; a polypeptide encoded by a nucleic acid consisting of a nucleotide sequence set forth in SEQ ID NO:1, 2 or 4; and a polypeptide encoded by a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides methods of modifying biological molecules based on the C-O bond formation activities of polypeptides derived from or related to a type II polyketide synthase (PKS) system capable of C-O bond formation, where the C-O bond forming activity of NonJ and NonK, two ketoacyl synthases present within the type II polyketide synthase system (PKS) responsible for biosynthesis of the macrotetralide nonactin have been identified (page 3). There are no indicia that the present application enables the full scope of the claims in view of the use of the sequences related to NonJ and NonK in the claimed methods as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the polypeptides consisting of an amino acid sequence set forth in SEQ ID NO:3 or 5 (reads the full length and fragments of SEQ ID NO:3 or 5); polypeptides encoded by a nucleic acid consisting of a nucleotide sequence set forth in SEQ ID NO:1, 2 or 4 (reads as a polypeptide encoded by the full length or a fragment of SEQ ID NO:1, 2 or 4); polypeptides encoded by a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation; and macrotetralides or macrotetralide analogs to be produced, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification has identified the C-O bond forming activity of NonJ and NonK in nonactin biosynthesis, where NonJ and NonK can act directly on acyl-CoA intermediates in catalyzing C-O bond formation (Fig. 5C), and wherein the amino acid sequences for NonJ and NonK set forth in SEQ ID NO:3 and 5, respectively; the nucleic acid sequences encoding NonJ and NonK are provided in SEQ ID NO:2 and 4, respectively; and SEQ ID NO:1 sets forth a partial nucleic acid sequence of the nonactin biosynthesis gene cluster including both NonJ and NonK genes; and the use of NonJ and NonK as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8-CoA to produce specific macrotetralides such as compounds **1-5** (Fig. 11; pages 32-49). However, the specification has not demonstrated the use of various biological molecules as substrates except for specific acyl-CoA to produce various macrotetralides, nor has identified any functional fragment of SEQ ID NO:3 or 5, and any functional polypeptide encoded by a fragment of SEQ ID NO: 1, 2 or 4, or a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Walczak et al., FEMS Microbiology Letters 183, 171-175 (2000)) teach the isolation and sequencing of 15559 bp of chromosomal DNA of nonactin biosynthsis gene cluster from S. grieseus, and indicates two of the genes, NonK and NonJ are unusual ketoacyl synthase (KAS)α and KASβ homologues. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the use of various biological molecules as substrates to produce various macrotetralides, and the identification of functional fragments of NonK and NonJ polypeptides, as well as the use of these peptides in the claimed method.

(4). Predictability or unpredictability of the art:

The claims encompass a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide sequence that are fragments or variants of NonK or NonJ. However, the use of various biological molecules as substrates to produce a macrotetralide and the identification of polypeptide sequence that are fragments or variants of NonK or NonJ are not adequately described in the specification, the invention is unpredictable regarding the sequences of functional peptides that fragments or variants of NonK or NonJ.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of modifying a biological molecule by formation of C-O bond, or a method of producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide sequence related to NonK or NonJ. The specification

has identified the C-O bond forming activity of NonJ and NonK in nonactin biosynthesis, and the use of NonJ and NonK as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8-CoA to produce specific macrotetralides such as compounds **1-5** (Fig. 11; pages 32-49). However, the specification has not demonstrated the use of various biological molecules as substrates except for specific acyl-CoA to produce various macrotetralides, nor has identified any functional fragment of SEQ ID NO:3 or 5, or any functional polypeptide encoded by a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4. Moreover, there are no working examples demonstrating the use of various biological molecules as substrates to produce various macrotetralides and various polypeptide sequence that are fragments or variants of NonK or NonJ in the claimed methods. Since the specification does not provide sufficient teachings on identification of functional polypeptide sequence that are fragments or variants of NonK or NonJ, and the use of various biological molecules as substrates to produce a macrotetralide, it is necessary to carry out undue experimentation to identify the functional peptide sequences that are fragments or variants of NonK or NonJ, and to use these peptides in the claimed methods.

(6). Nature of the Invention

The scope of the claim encompasses various biological molecules as substrates to produce a macrotetralide and various polypeptide sequences that are fragments or variants of NonK or NonJ, but the specification does not provide sufficient teachings on the identities and use of these substrates and peptide variants in the claimed methods. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods associated with variants, the teachings in the specification are limited, and the sequences of functional peptides are unpredictable, and therefore, it is necessary to carry out undue experimentation to identify the functional peptides and use of these peptides in the claimed methods.

Response to Arguments

Applicant indicates the factors in In re Wands have been discussed by the Examiner for the enablement rejection, however the claims have been amended to recite that the claimed polypeptide "consists" of the amino acid sequence set forth in SEQ ID NOs: 3 and 5 (respectively) and are encoded by nucleic acid sequences consisting of those identified as SEQ ID NOs: 1, 2, or 4; the specification specifically identifies "stringent conditions" under which hybridization occurs at pages 17 and 18; and the specification gives specific examples of the use of biological molecules as substrates being modified by forming C-O bond at, for example, the passages spanning page 49-65, which describes tests and assays for the identification of products that are modified by the formation of C-O bonds. Since claims 1, 2, 10, 17, 21, 23 and 25 and those dependent therefrom, no longer encompass sequences related to NonK or NonJ, thus the rejection should be withdrawn (pages 12-18 of the response).

Applicant's response has been fully considered, however, the arguments are not persuasive because of the following reasons. Although the amended claims recite a polypeptide consisting of an amino acid sequence set forth in SEQ ID NO:3 or 5; and a polypeptide encoded by a nucleic acid consisting of a nucleotide sequence set forth in SEQ ID NO:1, 2 or 4, the claims still read that the polypeptide contains fragments of SEQ ID NO:1-5 because of the use

"an amino acid sequence" instead of "the amino acid sequence". Furthermore, although claims recite a polypeptide encoded by a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation, the term "capable of C-O bond formation" indicates the peptide may have the activity of C-O formation, thus the peptide recited may or may not have the activity of C-O formation. Therefore, the claims still encompass the sequences that are fragments or variants of NonK or NonJ. Regarding the tests and assays for the identification of products that are modified by the formation of C-O bonds, although the specification teaches the identification of the product of formation of C-O bond, the specification does not provide sufficient teaching on the method steps in producing various macrotetralides or macrotetralide analogs using NonK or NonJ polypeptides, when the structures of macrotetralides or macrotetralide analogs are not defined. Thus, it requires undue experimentation to identify the functional fragments and variants of NonK or NonJ, and the use of NonK or NonJ polypeptides in the method of producing various macrotetralides or macrotetralide analogs. Therefore, the full scope of the claims is not enabled.

6. Claims 1-18 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-18 and 21-25 are directed to a method of modifying a biological molecule by formation of C-O bond, or producing a macrotetralide, comprising contacting a biological molecule (a substrate) with a polypeptide selected from the group consisting of: an amino acid

sequence set forth in SEQ ID NO:3 or 5; polypeptides encoded by a nucleic acid consisting of a nucleotide sequence set forth in SEQ ID NO:1, 2 or 4; polypeptides encoded by a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation. While the specification indicates that the instant application has identified the C-O bond forming activity of NonJ and NonK, two ketoacyl synthases present within the type II polyketide synthase system (PKS) responsible for biosynthesis of the macrotetralide nonactin, where NonJ and NonK can act directly on acyl-CoA intermediates in catalyzing C-O bond formation, and wherein the amino acid sequences for NonJ and NonK set forth in SEQ ID NO:3 and 5, respectively; the nucleic acid sequences encoding NonJ and NonK are provided in SEQ ID NO:2 and 4, respectively; and SEQ ID NO:1 sets forth a partial nucleic acid sequence of the nonactin biosynthesis gene cluster including both NonJ and NonK genes (page 3), the specification does not disclose a genus of variants for fragments of SEQ ID NO:3 or 5; polypeptides encoded by fragments of SEQ ID NO:1,2 or 4, or a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4 and capable of C-O bond formation; biological molecules as substrates being modified by forming C-O bond; and macrotetralides or macrotetralide analogs produced by using polypeptides that are fragments or variants of NonJ and NonK. Furthermore, the specification has not identified any fragment of SEQ ID NO:3 and 5 that is functional, and any functional polypeptide encoded by a nucleic acid fragment of SEQ ID NO;1, 2 or 4, or a nucleic acid that specifically hybridizes under various stringent conditions to SEQ ID NO:1, 2 or 4. The use of NonJ and NonK (SEQ ID NO:3 and 5) as ketoacyl synthases in catalyzing C-O bond formation between 6-CoA and 8-CoA to produce specific macrotetralides such as compounds **1-5** (Fig. 11) does not provide written description for

a genus of various biological molecules as substrates and various macrotetralides to be produced in the claimed method. Without guidance on structure to function/activity for fragments of SEQ ID NO:3 or 5 and polypeptides encoded by a nucleic acid fragment of SEQ ID NO;1, 2 or 4, or a nucleic acid that specifically hybridizes under stringent conditions to SEQ ID NO:1, 2 or 4, one skilled in the art would not know how to identify a functional polypeptide. The lack of description on structure to function/activity relationship of variant sequences of NonJ and NonK, and the use of these sequences to modify various biological molecules to produce various macrotetralides, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicant indicates claims 1, 2, 10, 17, 21, 23 and 25 have been amended to so as not to encompass any fragments of the recited sequences; the specification explicitly recites conditions and methods for hybridizing nucleotides at pages 17-18 and describes experiments for catalyzing C-O formation and methods for assaying for such; the specification gives examples of biological molecules used as substrates, namely 6-CoA and 8-CoA and methods for identifying the efficacy of the molecule as a substrate capable or being modified by C-O bond formation (at pages 49-65); and the specification does disclose the use of the invention to produce macrotetralides, as acknowledged by the Office, such as compounds 1-5 shown in Fig 1 and in Table 1 on page 64 of the specification. Thus, the invention is fully described in the specification providing a description of the use of the elements recited in the claims (pages 18-20).

Applicant's response has been fully considered, however, the arguments are not persuasive because of the following reasons. As indicated in the section above, the amended claims still encompass fragments and variants of NonJ and NonK, where the structure to function/activity relationship of variant sequences of NonJ and NonK is not described. Although the specification discloses the use of specific NonJ and NonK polypeptide (e.g., SEQ ID NO:3 and 5) to produce a specific macrotetralide (e.g., nonactin), the specification does not provide sufficient description on the production of various macrotetralides or macrotetralide analogs using NonJ and NonK polypeptide, which encompass numerous embodiments. The lack of description on the functional NonJ and NonK peptides and various macrotetralides, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 9, 10-16 and 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 10-16 are indefinite because the claim recites the term "a nucleic acid hybridizing under stringent conditions thereto". The cited term renders the claim indefinite, it is not clear what are these stringent conditions, e.g., are they highly stringent, or with medium or low stringency? Claims 11-16 are included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which they depend.

Response to Arguments

Applicant indicates claims 1, 2, 10, 17, 21, 23 and 25 have been amended to specifically recite that the conditions of hybridization are very stringent conditions as explicitly defined o page 18 of the specification. Further, the specification explicitly defines various conditions of stringency and wash conditions at, for example, pages 17-18 (page 20 of the response).

Applicant's response has been fully considered, however, the arguments are not persuasive because claim 10 does not recite a specific stringent condition defined at pages 17-18, thus the rejection maintained.

9. Claim 9, 16, 17 and 18 are indefinite as to how a macrotetralide or macrotetralide analog is produced since the claim only recites the step of forming C-O bond, but without including other coupling steps in the process, it is not clear how the final product of a macrotetralide is produced. Claim 18 is included in this rejection for being dependent on a rejected claim and not correcting the deficiency of the claim from which it depends.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
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CHIH-MIN KAM
PATENT EXAMINER

CMK
September 23, 2006